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Hemodynamic Control and Delirium

Jan Hirsch

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Abstract One of the adverse outcomes common in older surgical patients is postoperative delirium. The incidence of postoperative delirium varies depending on the type of patients studied, the tools used to measure delirium and the frequency of measurement. Although studies have identified predisposing and precipitating risk factors, to date, no single precipitating factor that can be modified by intraoperative anesthesia management has been found. Several studies identified intraoperative hypotension to be an important precipitating factor. However, this finding was not universally supported. Recent work on intraoperative blood pressure fluctuation and postoperative delirium may contribute to bridge this apparent discrepancy. These data indicate significantly larger intraoperative fluctuation in blood pressure in patients with postoperative delirium. Further research is needed to determine what type of patients are at risk for blood pressure lability and the effects of supporting blood pressure on the incidence of postoperative delirium.

Keywords Surgery · Blood pressure · Delirium · Hypotension · Hemodynamics · Perioperative complications

This article is part of the Topical collection on *Perioperative Delirium.*

J. Hirsch (✉)
Department of Anesthesia and Perioperative Care and Anesthesia Service, University of California San Francisco, San Francisco VA Medical Center, 4150 Clement Street Mail 129, San Francisco, CA 94121, USA
e-mail: jan.hirsch@ucsf.edu

Introduction

Aging of the general population results in a larger number of older patients undergoing major surgery. These patients tend to have more comorbidity; in particular, postoperative delirium is more common in this age group [1, 2, 3••, 4–6]. Delirium is characterized by inattention, abnormal level of consciousness, thought disorganization, and a fluctuating course [7, 8]. The reported incidence of postoperative delirium varies between 15 and 25 % [3••, 9, 10••, 11••], and the condition is frequently not recognized in clinical settings [10••]. Postoperative delirium is a serious problem for hospitalized geriatric patients [6, 10••, 12]. Postoperative delirium is associated with significant increases in functional disability, length of hospital stay, rates of admission to long-term care institutions, and rates of death [1, 6, 9, 13–21]. Patients who developed postoperative delirium required a hospital stay approximately four times longer than those who remained lucid [22]. More importantly, delirium resulted in three times increased rates of nursing home placement and was associated with two- to five-fold increases in complications and increases in hospital mortality rates of 10–65 % [8, 23–25]. In a recent study in elderly hip fracture patients, patients with postoperative delirium were found more likely to die, to be diagnosed with dementia or mild cognitive impairment, or to require institutionalization [26]. Furthermore, patients with more comorbidities, lower independence scores, a history of falls, and lower cognitive scores were significantly more likely to develop postoperative delirium in a recent study in 416 patients [20]. Postoperative delirium has been reported to occur soon after surgery [27], and the duration of postoperative delirium was an independent predictor of 6-months mortality in older adults after hip fracture in one study [28]. The economic burden has been estimated as more than $100 million per year, assuming an incidence of delirium of 20 % and annual hospitalizations of 11.8 million persons 65 years and older [29]. The pathophysiology of postoperative delirium is under active investigation [6, 15, 30, 31, 32•, 33]. Multiple causes have been proposed for delirium. For example, cholinergic deficiency [34] and the inflammation even from aseptic surgery [35–37] are considered important underlying pathophysiological mechanisms that render patients more susceptible to delirium in the perioperative period. While some recommendations such as avoiding deep anesthesia and supportive therapy have been published [30], this recommendation is controversial and no definitive prevention or therapy is currently available [6, 15, 31, 32•, 33]. Delirium has also been described to result from a disturbance of central tryptophan homeostasis [38, 39] and/or melatonin deficiency [40–45].

The current model suggested by Inouye [24] describes an interrelationship between predisposing and precipitating factors [15, 24, 46] on the development of delirium.

Predisposing Factors

In surgical and non-surgical patients, reported predisposing factors include advanced age, cognitive, functional and sensory impairment, depression, the number and severity of comorbidities, chronic renal insufficiency, abnormal glycemic control, dehydration, malnutrition, alcohol abuse, and sleep apnea [5, 47–57].

Precipitating Factors

Precipitating factors in the non-surgical setting include sleep disorders, sensory deprivation or overload, psychological stress, physical restraints, more than three medications added, a bladder catheter, and iatrogenic events [24, 58]. In surgical patients, precipitating perioperative factors include use of volatile anesthetics [6], opioids and benzodiazepines [6, 59], deep sedation [60], postoperative pain [61, 62], blood loss and decrease in intraoperative hematocrit [11••], intraoperative blood transfusion [11••, 63], and deep hypnotic state during anesthesia [30]. To date, no single precipitating factor that can be modified by intraoperative anesthesia management has been identified [6, 10••].

Physiologic Background

Cerebral blood flow in humans was first studied by Lassen [64] over 50 years ago. The underlying concept is known as cerebral autoregulation [64–66]. While there is an ongoing scientific debate regarding the mechanism of cerebral autoregulation [67, 68••], the thresholds based on this model are generally used in clinical practice [66]. Specifically, assuming constant carbon dioxide concentration, cerebral perfusion is maintained between 50 and 150 mmHg mean arterial pressure (MAP) during changes in cerebral perfusion pressure. Cerebral perfusion pressures below 50 mmHg may lead to cerebral hypoperfusion and can affect the functioning of neurons. Cerebral perfusion pressures and cerebral autoregulation may be compromised in patients with decreased elasticity of the arterial wall. Age alone has not been shown to have an influence on cerebral autoregulation [69], but conditions that occur more frequently in older patients may impede this mechanism. It has been demonstrated that hypertension increases the limits and decreases the efficiency of static and potentially of dynamic cerebral autoregulation [70–72], and that antihypertensive treatment diminishes the ability of the cerebral vasculature to compensate for drug-induced hypotensive episodes [73]. Moreover, cerebral blood flow responses have been shown to be affected by diabetes [74] and smoking [75], and an association of obstructive sleep apnea with a lower rate of recovery of cerebrovascular conductance for a given drop in blood pressure [76] has been determined. Other conditions encountered during anesthesia, such as hypercapnia [77, 78], patient position [79, 80], changes in the autonomous nerve system [81], or vasodilatation by medication [67, 82] may also affect cerebral autoregulation.

While quoted in current literature [66] and used in clinical practice, this model of cerebral autoregulation is probably at least overly simplistic [67, 68••]. Thresholds for the lower limit of autoregulation determined by other authors range from similar to substantially higher [67]. For example, Walsh recently published [73] a retrospective analysis in 33,330 patients on end-organ damage and established an empiric threshold of 55 mmHg based on data on acute kidney injury and myocardial infarction. The authors found a significantly increased stroke risk with intraoperative hypotension below a MAP of 55 mmHg.

Intraoperative Hypotension and Postoperative Delirium

In addition to the above precipitating factors, it has been proposed [6, 83••] that intraoperative hypotension is a major predictor of postoperative delirium, and avoiding intraoperative hypotension has been made part of a recently published intervention strategy [84].

Several recent studies concluded that, among other factors, intraoperative hypotension is a predictor of postoperative delirium (Table 1). Patti and coworkers reported that in 100 consecutive patients over 65 years of age undergoing colorectal surgery [3••], postoperative delirium rate was 18 % with significant associations with intraoperative hypotension, higher infusion volume, and more blood loss. In 90 consecutive urological surgery patients reported by Tognoni et al. [83••], age, preoperative cognitive and functional status, history of delirium, and hypotensive episodes during surgery were independent predictors of delirium. Aldemir et al. [9] conducted a prospective study in 818 consecutive critically ill patients who were admitted to the surgical intensive care unit. Of note, this study was performed in a general, younger population. Among the 90 patients with delirium, respiratory diseases, infections, anemia, hypotension, electrolyte abnormalities, and others were factors associated with delirium. Edlund et al. [85••] investigated 101 patients after femoral neck fracture before and after surgery and found that 18.8 % developed postoperative delirium, in this study [85••], 29.7 % of patients were delirious preoperatively, and all but one of the patients with preoperative delirium

Table 1 Published studies on postoperative delirium and hypotension

Study	No. of patients	Surgery	Age	Hypotension as risk factor	Other risk factors	Delirium risk	Remarks
Patti et al. [3••]	100	Colorectal surgery	>65	Yes	Higher infusion volume, blood loss, age, history of delirium, alcohol abuse, lower albumin, lower Barthel scores	18 %	
Tognoni et al. [83••]	90	Urological surgery	>65	Yes	Age, preoperative status, history of delirium	8.8 %	81 males and 9 females; 66 general, 22 spinal anesthesia
Aldemir et al. [9]	818	Critically ill	Adults	Yes	Respiratory diseases, infections, anemia, electrolyte abnormalities, male gender, age	11 %	Male/female (47/52 %), younger patients, intensive care setting. Critically ill, admitted to surgical intensive care unit, elective and emergency services
Edlund et al. [85••]	101	Femoral neck fracture	>65	Yes	Postoperative infections	48 %	Emergency surgery, 29.7 % delirious before surgery, 18.8 % postoperatively only
Echigoya et al. [86]	30	Elective laparotomy	n/a	Yes	Transfusion, infusion, surgery time, blood loss		Small sample size, limited statistics, article in Japanese
Gottesman et al. [87]	15	CABG	57–81	Yes	Preoperative mean arterial pressure	n/a	Small sample size, type of surgery may introduce additional covariate
Hirsch et al. [91••]	594	Major elective non-cardiac surgery	>65	No	Blood pressure fluctuation, age, female gender, lower preoperative cognitive score, longer surgery	30 % day 1, 29.6 % day 2	Patients undergoing general anesthesia
Williams-Russo et al. [88]	235	Elective total hip replacement	>50	No	Male sex, preoperative neuropsychology tests	Overall 7 %	Only epidural and spinal anesthesia, patients prospectively randomized to different MAP targets [45–55, 55–70 mmHg]. Overall Delirium risk 7, 9 % in low pressure, 4 % in higher BP group; no statistically significant difference
Marcantonio et al. [11••]	1,341	Major elective non-cardiac surgery	>50	No	Blood loss, more blood transfusions, postoperative Hct <30 %; age, function, cognitive impairment, alcohol, abnormal chemistry, surgery in multivariate analysis	9 %	All patients underwent general anesthesia, 55 % female
Santos et al. [90]	220	Coronary artery bypass graft surgery	>60	No	Age, blood urea, cardio-thoracic index, hypertension, smoking, blood transfusion, atrial fibrillation, pneumonia	33.3 %	Type of surgery may be an additional covariate

continued to have delirium after the surgery. Edlund found that patients with delirium had a higher incidence of perioperative falls in blood pressure.

In addition, two recent retrospective studies provide data on the hemodynamic data and postoperative cognitive status of 30 patients after abdominal surgery [86] and 15 patients after coronary artery bypass grafting [87], respectively. In both studies, the authors identified an association between intraoperative hypotension and postoperative delirium.

However, several large investigations reported contradictory results. In a prospective, randomized study on adults >50 years undergoing total hip replacement under epidural anesthesia, Williams-Russo et al. [88] demonstrated that hypotensive and normotensive patients had a similar incidence of postoperative cognitive dysfunction. Of note, this work only evaluated one single type of surgical procedure, and did not include patients undergoing general anesthesia. In a non-randomized, prospective clinical cohort study, Marcantonio et al. [11••] studied 1,341 patients over 50 years undergoing major elective non-cardiac surgery and found postoperative delirium in 117 patients (9 %). Route of anesthesia and intraoperative hemodynamic complications were not associated with delirium, while delirium was correlated with greater intraoperative blood loss, more postoperative blood transfusions, and postoperative hematocrit <30 %. Supporting these data, a large multicenter study found no association between intraoperative hypotension with short-term (1 week) or long-term postoperative cognitive dysfunction [89]. Similarly, a study in 220 patients after coronary artery bypass grafting [90] did as well not find an influence of intraoperative perfusion pressure on postoperative delirium.

We recently performed a prospective cohort study of 594 patients aged ≥65 years after non-cardiac surgery [91••]. In this elderly cohort, 178 patients (30 %) developed delirium on day one and 176 (29.6 %) on day two after surgery. At baseline, patients with delirium were significantly older, more often female, had lower preoperative cognitive scores, and underwent longer operative procedures. Relative hypotension (decreases by 20, 30, or 40 %) or absolute hypotension (MAP <50 mmHg) was not significantly associated with postoperative delirium, nor was the duration of hypotension (MAP <50 mmHg). Conversely, intraoperative fluctuations in blood pressure (measured by the variance) were significantly associated with postoperative delirium [91••].

A Potential Role for Blood Pressure Fluctuation

Blood pressure fluctuation, measured by variance, may provide an explanation for this apparent discrepancy in study results. We observed larger intraoperative fluctuation in blood pressure in patients who later developed postoperative delirium [91••]. Different from hypotension, the calculation of blood pressure variance includes both blood pressure increases and decreases throughout the entire course of surgery. After controlling for demographic factors, blood pressure variance remained a significant factor for the development of postoperative delirium [91••]. In multivariate analysis, preoperative cognitive status and length of surgery in combination with hemodynamic variance contributed to postoperative delirium. Other factors, such as age, may indirectly contribute to larger intraoperative fluctuations in intravascular volume and blood rheology in these patients.

Recent work has suggested that visit-to-visit blood pressure variability may be associated with cardiovascular and stroke risk [92, 93]. While the hypothesis of an association of this finding with our results on postoperative delirium may look appealing, many other surgical and anesthetic factors may contribute to both intraoperative and inter-visit blood pressure variability. For example, intraoperative blood loss, intravascular volume shifts, surgical stimulation, or anesthesia medication may contribute to intraoperative blood pressure variability, while medication compliance may affect visit-to-visit variability.

Challenges in Determining the Role of Intraoperative Blood Pressure

In our study [91••], few patients had substantial blood pressure decreases, which emphasizes that intraoperative hypotension is not an independent variable, but tightly controlled by the anesthesiologist. In addition, intraoperative hypotension is related to variables such as intraoperative blood loss and transfusion, which have been shown to be associated with postoperative delirium [63]. Moreover, some investigators found that episodes of intraoperative hypotension may be enhanced (or obscured) by reporting bias if manual data entry versus automatic blood pressure recording is used [94].

Conclusions

Postoperative delirium is a geriatric syndrome with unknown etiology. Currently, there are conflicting data if blood pressure decreases during surgery are associated with a significantly increased risk of this condition. Moreover, recent work indicates that blood pressure fluctuations during surgery, represented by changes in blood pressure variance, contribute to early postoperative delirium. Additional research is needed to predict which patients may have a greater tendency toward developing lability in blood pressure during surgery. The evidence to date suggests that prospective clinical trials are needed to determine if even tighter control of intraoperative blood pressure to minimize hypotension and fluctuation will lead to a decreased incidence in postoperative delirium.

Compliance with Ethics Guidelines

Conflict of Interest Jan Hirsch declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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